

We Claim:

1. A method for achieving high sensitivity detection and/or high accuracy quantitation of a target protein in a biological sample, comprising:
 - (1) providing two or more different capture agents for detecting a target protein in
 5 a test sample, which capture agents are provided as an addressable array, and each of which capture agents selectively interacts with a peptide epitope tag (PET) of said target protein;
 - (2) contacting said array with a solution of polypeptide analytes produced by denaturation and/or cleavage of proteins from the test sample;
 - 10 (3) detecting the presence and amount of said target protein in the sample from the interaction of said polypeptide analytes with each said capture agents;
 - (4) quantitating, if present, the amount of the target protein in the sample by averaging the results obtained from each said capture agents in (3).
2. The method of claim 1, wherein each said different capture agents specifically bind a
 15 different PET of said target protein.
3. The method of claim 2, wherein said different capture agents belong to the same category of capture agent.
4. The method of claim 3, wherein said category of capture agent includes: antibody,
 20 non-antibody polypeptide, PNA (peptide nucleic acids), scaffolded peptide, peptidomimetic compound, polynucleotide, carbohydrates, artificial polymers, plastibody, chimeric binding agnet derived from low-affinity ligand, and small organic molecules.
5. The method of claim 2, wherein at least two of said different capture agents belong to
 25 different categorys of capture agent selected from antibody, non-antibody polypeptide, PNA (peptide nucleic acids), scaffolded peptide, peptidomimetic compound, polynucleotide, carbohydrates, artificial polymers, plastibody, chimeric binding agnet derived from low-affinity ligand, and small organic molecules.
6. The method of claim 1, wherein a subset of said capture agents bind to the same PET,
 30 and wherein each capture agents of said subset belong to different category of capture agent selected from: antibody, non-antibody polypeptide, PNA (peptide nucleic acids), scaffolded peptide, peptidomimetic compound, polynucleotide, carbohydrates, artificial polymers, plastibody, chimeric binding agnet derived from low-affinity ligand, and small organic molecules.

7. The method of claim 1, wherein said target protein has two or more different forms within said biological sample.
8. The method of claim 7, wherein said different forms include unprocessed / pro-form and processed / mature form.
- 5 9. The method of claim 7, wherein said different forms include different alternative splicing forms.
10. The method of claim 7, wherein said different forms include unmodified and post-translationally modified form with respect to one or more post-translational modification(s).
- 10 11. The method of claim 10, wherein said post-translational modification includes: acetylation, amidation, deamidation, prenylation, formylation, glycosylation, hydroxylation, methylation, myristoylation, phosphorylation, ubiquitination, ribosylation and sulphation.
12. The method of claim 7, wherein a subset of said capture agents are specific for
15 PET(s) only found in certain forms but not in other forms.
13. The method of claim 12, further comprising determining the percentage of one form of said target protein as compared to the total target protein, or ratio of a first form of said target protein to a second form of said target protein.
14. The method of claim 1, further comprising detecting other target proteins within said
20 biological sample with capture agents specific for PETs of said other target proteins.
15. The method of claim 14, wherein two or more different capture agents are used for detecting and/or quantitating at least one of said other target proteins.
16. The method of claim 1, wherein, for each capture agent, the method has a regression coefficient (R^2) of 0.95 or greater.
- 25 17. The method of claim 1, wherein the array has a recovery rate of at least 50 percent.
18. The method of claim 1, wherein the accuracy is 90%.
19. The method of claim 1, wherein said sample is a body fluid selected from: saliva, mucous, sweat, whole blood, serum, urine, amniotic fluid, genital fluid, fecal material, marrow, plasma, spinal fluid, pericardial fluid, gastric fluid, abdominal
30 fluid, peritoneal fluid, pleural fluid, synovial fluid, cyst fluid, cerebrospinal fluid, lung lavage fluid, lymphatic fluid, tears, prostatitic fluid, extraction from other body

parts, or secretion from other glands; or from supernatant, whole cell lysate, or cell fraction obtained by lysis and fractionation of cellular material, extract or fraction of cells obtained directly from a biological entity or cells grown in an artificial environment.

- 5 20. The method of claim 1, wherein said sample is obtained from human, mouse, rat, frog (*Xenopus*), fish (zebra fish), fly (*Drosophila melanogaster*), nematode (*C. elegans*), fission or budding yeast, or plant (*Arabidopsis thaliana*).
21. The method of claim 1, wherein said sample is produced by treatment of membrane bound proteins.
- 10 22. The method of claim 1, wherein step (3) is effectuated by directly detecting and measuring captured PET-containing polypeptides using mass spectrometry, colorimetric resonant reflection using a SWS or SRVD biosensor, surface plasmon resonance (SPR), interferometry, gravimetry, ellipsometry, an evanescent wave device, resonance light scattering, reflectometry, a fluorescent polymer
15 superquenching-based bioassay, or arrays of nanosensors comprising nanowires or nanotubes.
23. The method of claim 1, wherein step (3) is effectuated by using secondary capture agents specific for captured polypeptide analytes, wherein said secondary capture agent is labeled by a detectable moiety selected from: an enzyme, a fluorescent label,
20 a stainable dye, a chemiluminescent compound, a colloidal particle, a radioactive isotope, a near-infrared dye, a DNA dendrimer, a water-soluble quantum dot, a latex bead, a selenium particle, or a europium nanoparticle.
24. The method of claim 23, wherein said secondary capture agent is specific for a post-translational modification.
- 25 25. The method of claim 24, wherein said secondary capture agent is a labeled secondary antibody specific for phosphorylated tyrosine, phosphorylated serine, or phosphorylated threonine.
26. The method of claim 1, wherein said sample contains billion molar excess of unrelated proteins or fragments thereof relative to said target protein.
- 30 27. The method of claim 1, wherein said PET is identified based on one or more of the protein sources selected from: sequenced genome or virtually translated proteome, virtually translated transcriptome, or mass spectrometry database of tryptic fragments.
28. The method of claim 1, wherein the target protein is a biomarker with a concentration of about 1-5 pM in said sample.
- 35 29. The method of claim 1, wherein the target protein is a biomarker with relatively small

concentration change of no more than 50%, 40%, 30%, 20%, 10%, 5%, or 1% in a disease sample.

30. An array of capture agents for detecting and quantitating a target protein within a biological sample, comprising a plurality of capture agents, each immobilized on a distinct addressable location on solid support, each of said capture agents specifically binds a PET uniquely associated with a peptide fragment of said target protein that predictably results from a treatment of said biological sample.
31. The array of claim 30, wherein said solid support is beads or an array device in a manner that encodes the identity of said capture agents disposed thereon.
32. The array of claim 29, wherein said array includes 2 - 100 or more different capture agents.
33. The array of claim 29, wherein said array device includes a diffractive grating surface.
34. The array of claim 29, wherein said capture agents are antibodies or antigen binding portions thereof, and said array is an arrayed ELISA.
35. The array of claim 29, wherein said array device is a surface plasmon resonance array.
36. The array of claim 29, wherein said beads are encoded as a virtual array.
37. A composition comprising a plurality of capture agents, wherein each of said capture agents recognizes and interacts with one PET of a target protein.
38. The composition of claim 37, wherein said capture agents is independently selected from: antibody, non-antibody polypeptide, PNA (peptide nucleic acids), scaffolded peptide, peptidomimetic compound, polynucleotide, carbohydrates, artificial polymers, plastibody, chimeric binding agent derived from low-affinity ligand, and small organic molecules.
39. The composition of claim 38, wherein said capture agents are antibodies, or antigen binding fragments thereof.
40. The composition of claim 39, wherein said capture agent is a full-length antibody, or a functional antibody fragment selected from: an Fab fragment, an F(ab')₂ fragment, an Fd fragment, an Fv fragment, a dAb fragment, an isolated complementarity determining region (CDR), a single chain antibody (scFv), or derivative thereof.
41. The composition of claim 39, wherein each of said capture agents is a single chain antibody.